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Carotid intima-media thickness (cIMT) and plaque from risk assessment and clinical use to genetic discoveries

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Summary Carotid intima—media thickness (cIMT) and carotid plaque are ultrasound imaging measures of carotid atherosclerosis and strong predictors of future stroke, myocardial infarction and vascular death. The use of ultrasound measures of cIMT and carotid plaque as a screening tool in clinical practice however have been extremely limited by a lack of recognition of its value by medical communities, health care policy makers and a lack of reimbursement by third-party payers engaged in the delivery of vascular imaging services. This review addresses the role of cIMT and plaque in vascular disease risk prediction. Recent data from large population based studies on reclassification of the vascular risk using carotid ultrasound imaging markers is presented. In addition, the common clinical scenarios for the appropriate use of cIMT in clinical setting are summarized according to the recent study conducted by the Society of the Atherosclerosis Imaging and Prevention in collaboration with the International Atherosclerosis Society. This presentation is intended to provide a practical guide for use of cIMT and plaque to clinicians to promote optimal clinical use of cIMT and to researchers to direct cIMT and plaque research towards investigating environmental and genetic factors of a complex disorder — subclinical atherosclerosis — leading to future genetic discoveries and new anti-atherosclerotic therapies.

Introduction

Atherosclerosis is a complex inflammatory process underlying the occurrence of heart attacks and most ischemic strokes. Traditional vascular risk factors are important for development of atherosclerosis but interestingly, explain only about 50% of the risk of cardiovascular disease (CVD) and stroke. Current screening strategies are based on these risk factors. However the complexity of stroke and CVD has led to the increasing use of intermediate phenotypes in risk prediction of vascular disease and surrogate outcomes in clinical trials. *Carotid intima—media thickness (cIMT) and carotid plaque* are widely used as intermediate, preclinical phenotypes of vascular disease (Fig. 1). Although individuals with subclinical atherosclerosis have not yet experienced overt vascular disease, they have a greater risk for incident stroke and MI in comparison to individuals without

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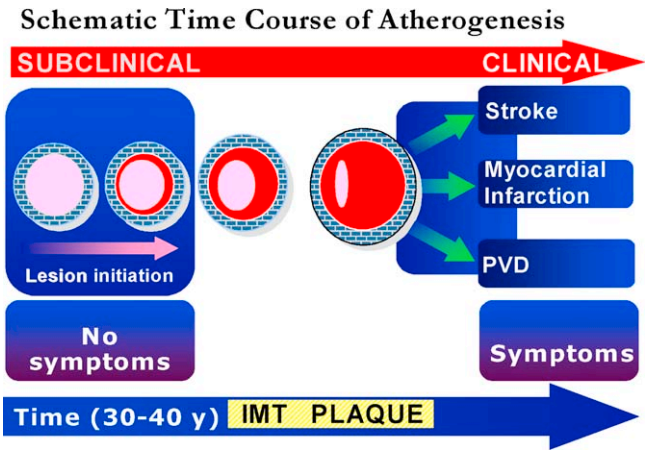

Figure 1 Schematic time course of atherogenesis.

evidence of increased subclinical atherosclerotic disease. Carotid ultrasound imaging measures of carotid plaque and cIMT are proposed as surrogate markers of CVD and stroke as objective indicators of the biological and pathobiological processes of atherosclerosis. They can also serve as surrogate endpoints for clinical vascular outcomes based on epidemiologic, therapeutic, pathophysiologic and other scientific evidence. This review article will provide an overview on the relevant literature regarding the use of cIMT and carotid plaque as surrogate markers in various research investigations and clinical practice.

What is carotid intima—media thickness (cIMT)?

Carotid IMT is a widely accepted imaging surrogate marker of generalized atherosclerosis [1,2]. On ultrasound, cIMT is represented by a double-line pattern on the near and the far wall of the carotid artery (Fig. 2). The two anatomical landmarks which can be measured as the double-line pattern are the lumen—intima and the media—adventitia interfaces [3]. Even without presence of atherosclerosis the intima and the media layer increase with advancing age as a result of adaptive changes to biomechanical parameters, like blood flow and tension on the wall [4]. Since these changes give rise to molecular and cellular pathways, which are also involved in the formation of atherosclerotic plaque, cIMT is related to subclinical atherosclerosis, but should not be used synonymously [5]. According to large studies, such as *The Atherosclerosis Risk in Communities* (ARIC) study, *The Cardiovascular Health Study* (CHS), and *The Rotterdam* study, a correlation between cIMT measurements and risk of cardiovascular events has been established [1,4,6]. Inversely, a connection between the reduction of intima—media progression with lipid-lowering therapies and a reduction of cardiovascular risk shown in clinical trials [7,8] has lead to considering cIMT a surrogate end point for the effect of anti-atherosclerotic therapy [9]. This is an important fact for risk evaluation since cIMT appears at an early stage of atherosclerosis when alterations in treatment can substantially change the course of the disease more effectively. The advantage of measuring the cIMT by high resolution B-mode ultrasonography lies in its rapidly applicable and available, non-invasive and cost-effective nature [3]. Progression of cIMT is therefore an attractive method for use in research as it can be easily assessed to study vascular risk or the therapeutic effects of a specific treatment. Nevertheless, evidence considering cIMT as a surrogate marker for CVD is still a matter of debate [2,10—12].

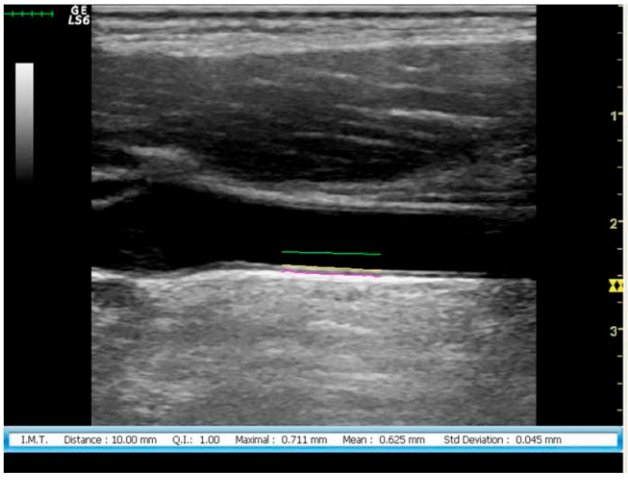

Figure 2 Assessment of carotid IMT.
Measurement of the IMT in the far wall of the common carotid artery (CCA) with an IMT mean of 0.625 ± 0.045 mm. IMT was measured by an automatic edge detection algorithm as represented by the yellow and purple lines (the green line in the lumen of the CCA represents the reference value for the arterial wall echo gradient calculations).

What is atherosclerosis?

In order to understand the distinctive nature of cIMT and carotid plaque in the risk of stroke and CVD the process of atherosclerosis has to be clearly understood. About 10—20% of ischemic strokes are due to large artery atherosclerosis, mainly located in the extracranial arteries [13]. Atherosclerotic process leads to luminal stenosis, flow restriction and plaque rupture and is therefore a strong predictor of ischemic stroke [14]. Atherosclerosis is a chronic inflammatory process, involving endothelial injury, activation and recruitment of immune-inflammatory cells, smooth muscle cell proliferation, and influx of lipoprotein [15]. Various mediators like chemokines, cytokines, growth factors, proteases, adhesion molecules, hemostasis regulators, and their interactions are involved in the process of plaque growth. Proinflammatory signaling is triggered by oxidized low-density lipoprotein (LDL) or through alterations and remodeling in the extracellular matrix [9,16]. This process leads to different plaque composition with variable vascular risk due to different susceptibility for plaque rupture resulting in artery-to-artery embolization. Depending on the stage of the atherosclerotic changes in the vessel wall there is a variety in plaque morphology. It differs from homogeneous thickening of the wall to hyperechogenic components consisting mainly of fibrous tissue and calcification, and hypoechogenic components representing areas with atheromatous material like lipid deposits, cell debris and necrotic material. Hypoechogenic components are considered more harmful due to their instability [17]. Atherosclerosis predominantly develops at specific sites in the vessel, mainly

areas with altered blood flow, like bifurcations, branch points and areas of vessel curvature. The mass transport and the shear stress theory are two hypotheses about flow regulated mechanical forces contributing to atherosclerosis. In case of the first theory a low or disturbed blood flow results in an increased uptake of bioactive substances into the vessel wall, whereas in the latter theory mechanical forces of blood flow on the vessel wall, called shear stress, play an important role in protection of endothelial function [16].

Surrogate markers of atherosclerosis

According to the NIH Definition Working Group, surrogate markers act as a substitute for a clinical end point and should be able to predict the desired clinical benefit, respectively the lack of benefit, or harm, based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence [18]. Biological markers are objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic response to a therapeutic intervention. The clinical end point is defined as a variable that reflects how the patient feels, functions, or survives. Alteration of these markers should be displayed in a change of a clinically relevant end point [9]. The interest to use surrogate markers in order to assess the effectiveness of a treatment is increasing rapidly. Traditional biomarkers like blood pressure and serum cholesterol are used widely for risk assessment and in the development of treatment. Despite effective treatments of traditional risk factors, a large number of individuals experience CVD, which shows the need for investigations of other surrogate markers to help in the search for novel therapies [9].

There are numerous risk factors, which are currently used for the screening of atherosclerosis. Besides traditional vascular risk factors like high blood pressure, diabetes, smoking, stress, obesity, and metabolic syndrome, there is a growing list of less traditional and soluble markers such as high LDL or low HDL, CRP, LP (a), homocysteine, LDL particle size, Lp-PLA2, ApoB/ApoA [19]. Additionally, screening for atherosclerosis can be accomplished by imaging methods for arterial structure or function. Among the imaging methods for arterial structure, ultrasound measures of cIMT and plaque are most widely used. Furthermore, aortic and carotid plaque can be assessed by MRI, and the coronary calcium score by electron beam CT (EBCT) [20,21]. Brachial vasoreactivity measured by ultrasound, vascular compliance measured by radial tonometry and microvascular reactivity measured by fingertip tonometry are examples of arterial function tests that have been rapidly developing for the assessment of subclinical atherosclerosis [22,23].

Blood pressure and LDL-cholesterol are FDA-approved surrogate markers of cardiovascular disease while ultrasound measure of cIMT is still awaiting its final approval and validation by the FDA [3,9].

Carotid IMT in epidemiological studies and clinical trials

Carotid IMT has been associated with increased risk of cardiovascular events in large epidemiological studies. In a systematic review and meta-analysis, eight observational population-based studies were examined and showed the significant association of cIMT with risk of CVD [2]. Based on the data from general population, cIMT showed a slightly higher risk for stroke (hazard ratio, HR 1.32; 95% CI, 1.27−1.38) than for myocardial infarction (HR 1.26; 95% CI, 1.21−1.30). However, there are limitations to the interpretation of these results, especially concerning variable methodology, e.g. difference in definitions of carotid segments or the way the measurements were reported. Therefore the importance of following standardized cIMT protocols is emphasized for future studies.

In the clinical trials, a systematic review and meta-analysis of the effect of LDL-lowering by statins on the change of cIMT was examined [24]. Analysis of nine lipid-lowering trials showed a strong correlation between reduction of LDL and cIMT, with each 10% reduction in LDL-cholesterol accounting for a reduction of cIMT by 0.73% per year.

Although the association of cIMT and increased risk of cardiovascular events has been established, there is still a lack of sufficient evidence to show whether lowering of cIMT will translate in the reduction in CVD. Furthermore, subclinical atherosclerosis is to some extend considered a non-causal and nonspecific marker of atherosclerotic complications [2,25]. Diverse approaches for measuring cIMT and a lack of unified criteria for distinguishing early plaque formation from thickening of the cIMT might contribute to the fact of missing evidence on risk prediction. The implementation of standardized methods in the measurement of cIMT is necessary for further investigations since cIMT depicts early atherosclerosis as well as nonatherosclerotic compensatory enlargement, with both phenotypes having a different impact on predicting vascular events [3,25].

Does carotid IMT add to prediction of CVD beyond traditional risk factors?

Current studies on the effect of cardiovascular risk factors in conjunction with measures of atherosclerosis (cIMT and plaque) on risk prediction indicate a small but incremental effect for risk prediction of CVD. In the recent analysis from the community-based ARIC study among 13,145 subjects, approximately 23% individuals were reclassified into a different risk category group after adding information on cIMT and carotid plaque [11]. Adding cIMT to traditional risk factors provided the most improvement in the area under the receiver-operating characteristic curve (AUC), which increased from 0.74 to 0.765. Adding plaque to the cIMT and traditional risk factors had however the best net reclassification index of 10% in the overall population. In the Cardiovascular Health Study, another population-based study among 5888 participants, the elevated CRP was associated with increased risk for CVD only among those individuals who had increased cIMT and plaque detectable on carotid ultrasound. Despite these significant associations with CVD, CRP, cIMT and plaque only modestly improved the prediction of CVD outcomes after accounting for the traditional risk factors [26]. Addition of CRP or subclinical carotid atherosclerosis to conventional risk factors resulted in a modest increase in the ability to predict CVD. In the

NOMAS population, presence of carotid plaque considerably contributed to the better estimation of 10-year Framingham vascular risk [14]. More than a half of individuals in low and moderate FRS categories were reclassified into the higher risk category if carotid plaque was present. Traditional CVD risk prediction schemes need further improvement and cIMT and plaque may help improve CVD risk prediction with a direct implication for the risk stratification and treatment in vascular preventive programs.

Carotid IMT in different carotid artery sites

The localization of atherosclerosis is determined by hemodynamic forces, like shear stress and tensive forces, and additional local predisposing factors [27]. Since these local factors and hemodynamical forces are distributed variably in the carotid vessels there are differences in the distribution and development of cIMT. A population-based study on the association of IMT at various sites and cardiovascular risk factors showed that IMT in the common carotid artery (CCA IMT) is correlated with risk factors for stroke and prevalent stroke. Conversely, intima—media thickness in the bifurcation, together with carotid plaque, were more directly associated with risk factors of ischemic heart disease and prevalent ischemic heart disease [28]. Systolic blood pressure seems to be the most important factor influencing IMT in the common carotid artery, whereas smoking may be more important for IMT in the internal carotid artery (ICA IMT). Both sites of IMT were independently associated with prevalent CVD, with the ICA IMT having a larger area under the ROC (receiver operating characteristic) curve than CCA IMT (0.756 vs. 0.695) [29]. Furthermore, evidence from a population-based study showed variation in the progression of IMT at different arterial sites [30]. Progression rate of ICA IMT was significantly greater compared to IMT in the bifurcation or in the common carotid artery. In addition, ICA IMT correlated better with vascular risk factors than CCA IMT. The results suggest that ICA IMT might be a better measure of CVD than the more frequently investigated CCA IMT.

Carotid atherosclerotic plaque vs. cIMT

Carotid plaque is a distinctive phenotype of atherosclerosis [14]. Carotid IMT, however, is mainly related to hypertension resulting in a hypertrophy of the media layer of the vessel wall [31]. There is evidence of genetic influence on cIMT, whereas carotid plaque is strongly influenced by environmental factors [14,32]. Although cIMT has been associated with increased risk of cardiovascular disease, carotid plaque is a stronger predictor of cardiovascular disease in large population-based studies [33]. Nevertheless, differentiation of early plaque formation from increased cIMT is hard to determine. Although cIMT and plaque share the effect of atherosclerotic risk factors, they have different natural history, patterns of risk factors, and the prediction of vascular events. Since definition of carotid plaque varies, various professional organizations have proposed a standard plaque definition. According to the Mannheim consensus, plaque is defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrates a thickness >1.5 mm as measured from the media—adventitia interface to the intima—lumen interface [3].

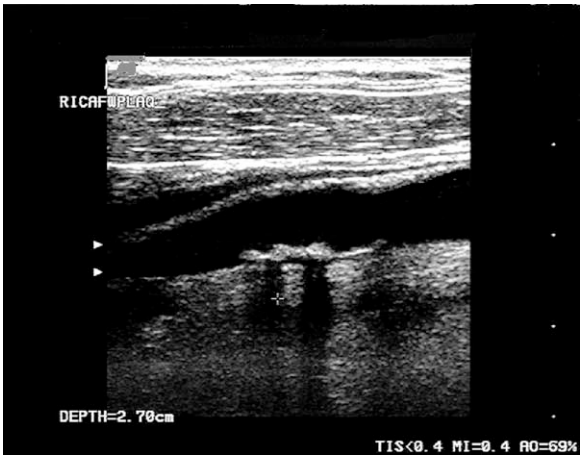

Figure 3 Calcified carotid plaque.

Besides presence and plaque size, plaque composition or morphology may be a better predictor or marker of vascular events [34]. Atherosclerosis, including plaque formation, represents a dynamic process involving a complex cascade of inflammatory events from lipid deposition to plaque calcification [35]. There is conflicting evidence about the effect of calcified carotid plaque on cardiovascular events [34,36—38]. Echolucent, fatty plaques are considered more harmful, since they are less stable and therefore more prone to rupture [39]. Individuals with calcified or echodense plaque on the other hand, are less likely to have symptomatic disease [40]. In contrast, a significant association between presence of carotid plaque calcification (Fig. 3.) and increased risk of vascular events was reported in a large population based study [41].

Calcified plaque appeared to be a significant predictor of combined vascular outcomes with a HR of 2.4 [95% CI, 1.0—5.8] when compared to absence of plaque and after adjusting for demographics, mean cIMT, education and risk factors. Another study evaluated the risk of cardiovascular events in the presence of plaque surface irregularities. Irregular plaque surface increased the risk of ischemic stroke by 3-fold. The cumulative 5-year risk for ischemic stroke was over 8% for those with irregular plaque surface compared to those with regular plaque (<3%) [13]. Superficial calcification has been shown to play a role in instability of atherosclerotic plaque [42]. Whether soft, calcified and irregular plaques are different stages of the same process or separate entities is a matter of controversy and longitudinal studies with careful assessments of plaque progression are needed to resolve these issues.

Carotid plaque and risk of CVD in epidemiological studies

Small, non-stenotic carotid plaque is associated with an increased risk of stroke and other vascular events [14]. The predictive power of presence of carotid plaque has been demonstrated in several large observational studies

[13,37,43—45]. In the *Atherosclerosis Risk in Communities* study, a large population based study on 13,123 participants with a mean follow up of 8 years, the presence of carotid plaque was associated with a 2-fold increased risk of ischemic stroke [37]. Carotid plaque was associated with a 1.7-fold increased risk of incident stroke in the *Cardiovascular Health Study* [46] over a mean follow-up time of 3.3 years and with a 1.5-fold increased risk in the *Rotterdam* Study [45] over a mean follow-up time of 5.2 years. In the *Northern Manhattan Study* (NOMAS), presence of plaque was associated with a 2.8-fold [HR 2.76, 95% CI, 2.1—3.63] increased risk of stroke, MI and vascular death during a mean follow up of 6.9 years [14]. Comparison between these studies however is limited due to diverse study populations and different measuring methods of atherosclerotic plaque [14].

Carotid plaque area may be a better measure of atherosclerosis than cIMT or plaque thickness, since evidence suggests that plaque area grows at a double rate in average than it thickens [47]. In the Tromso study, another large population based study, total plaque area was a stronger predictor for the incident ischemic stroke than cIMT [31]. In 3240 men and 3444 women ultrasonographic assessment of plaque area resulted in a HR of 1.23 (95% CI, 1.09—1.38) in men and 1.19 (95% CI, 1.01—1.41) in women for 1 SD increase in square-root-transformed plaque area when adjusted for other cardiovascular risk factors. The multivariable-adjusted HR in the highest quartile of plaque area versus no plaque was 1.73 (95% CI, 1.19—2.52) in men and 1.62 (95% CI, 1.04—2.53) in women. The multivariable-adjusted HR for 1 SD increase in IMT was 1.08 (95% CI, 0.95—1.22) in men and 1.24 (95% CI, 1.05—1.48) in women [31].

Why carotid IMT and plaque are not commonly accepted surrogate endpoints?

A recent large meta-analysis of 18 case—control and cohort studies evaluated the value of cIMT and plaque in the screening for coronary heart disease [10]. It included 2920 individuals with CHD and 41,941 without CHD and showed no benefit of these parameters as a screening tool, since the discrimination between affected and unaffected individuals was insufficient. Similarly, another recent meta-analysis of 41 randomized trials showed that regression or slowed progression of cIMT with cardiovascular drugs did not affect the risk of cardiovascular events [12].

This evidence indicated that cIMT may not completely meet all criteria of a surrogate marker. A marker should be sensitive, available, non-invasive, and easy to evaluate; all of which are characteristics of cIMT and carotid plaque. However, a causal relationship with the clinical outcome would need to be established and these evidences are likely to come from large longitudinal studies in low risk individuals as well as from basic science research. Furthermore, to act as a surrogate marker cIMT should be able to reflect the full therapeutic effect on the clinical outcome which has not been show yet [48]. Some new information will come from an ongoing large multinational meta-regression study investigating individual progression rate of cIMT and risk of vascular outcomes [49].

Who should be screened for carotid IMT and plaque? Current guidelines/appropriate and not appropriate indications

With increasing incidence of CVD and stroke in the population it is important to identify high-risk patients with subclinical manifestation of disease which will benefit from early and aggressive therapy. The Mannheim cIMT consensus states that there is no need to 'treat IMT values' nor to monitor IMT values in individual patients apart from few exceptions [3,50]. The current guideline for the use of carotid IMT in assessment of cardiovascular risk in asymptomatic adults from 2010 gives carotid IMT class IIa rank with a level B for evidence for asymptomatic adults at intermediate risk. They emphasize the importance of following clear recommendations on the use of appropriate scanning and reading imaging ultrasound methodology [51]. Accordingly, the American Society of Echocardiography recommends in their *consensus statement*, the use of carotid IMT assessment should be reserved for individuals with intermediate cardiovascular risk with; e.g. at a 6—20% 10-year risk of cardiovascular disease according to the Framingham Risk Score (FRS). Since some high-risk groups might not be addressed by this approach, there are further clinical circumstances that should be considered: (1) family history of premature CVD in first-degree relative (men <55 years old, women <65 years old); (2) individuals younger than 60 years old with severe abnormalities in a single risk factor (e.g., genetic dyslipidemia) who otherwise would not be candidates for pharmacotherapy; or (3) women younger than 60 years old with at least two CVD risk factors [5].

Appropriate use of measuring carotid IMT in the clinical setting was examined and summarized by the *Society of Atherosclerosis Imaging and Prevention* and the *International Atherosclerosis Society* [52]. To prevent either under- or over-utilization of IMT-measurements, common clinical scenarios, including risk assessment in the absence of known coronary heart disease (CHD), risk assessment in patients with known CHD, and serial carotid IMT imaging for monitoring of CHD risk status, were rated. The conclusion of these professional organizations was that appropriate indications for the use of cIMT is for individuals without CHD with intermediate risk, older, and individuals with metabolic syndrome. The testing of low-risk or very high-risk CHD individuals as well as serial cIMT testing is considered inappropriate use of this method.

Beginning of genetic discoveries

Common vascular risk factors like hypertension, diabetes, hypercholesterolemia, and nicotine play an important role in the development of atherosclerosis. Therefore, the treatment and control of these factors is a major target in prevention of stroke. However, these environmental risk factors contribute only to about half of all cases of atherosclerotic disease [53]. Finding novel risk factors of atherosclerosis is of great importance for prevention of cardiovascular disease [17]. The focus of preventing strategies tends to shift towards the investigation of genetic factors.

Variation in cardiovascular risk in the population is likely to be connected to variability in genes that are involved in the endothelial inflammatory response to oxidized lipids [17]. Identifying factors underlying the variation of subclinical atherosclerosis unexplained by traditional vascular risk factors either deleterious or protective may help targeting preventive strategies. As opposed to traditional thinking, we have found that the traditional vascular risk factors explain only 21% of the variance in the total carotid plaque burden in a multi-ethnic population of NOMAS. The most explanatory risk factors include age, sex, pack-years of smoking, systolic blood pressure, diastolic blood pressure, antihypertensive and lipid-lowering medications, and diabetes mellitus status. An inclusion of less traditional risk factors such as LDL:HDL ratio, homocysteine levels, high school completion, white blood cell count and LDL cholesterol to the traditional model contributed only about additional 2%, explaining 23% of the variance in total carotid plaque burden at best. Therefore variation in subclinical carotid plaque burden is largely unexplained by known vascular risk factors. These results suggest that other unaccounted factors, both environment and genetic, play an important role in the determination of subclinical atherosclerosis. Identification of these genetic and environmental factors underlying unexplained subclinical atherosclerosis is of great importance for successful prevention of stroke and cardiovascular disease, and is in the major focus for future investigations leading to genetic discoveries and new anti-atherosclerotic treatments.

Conclusion

Carotid IMT and carotid plaque are significant predictors of vascular events and 2D ultrasound measurement of cIMT and carotid plaque is an inexpensive way to detect individuals with increased atherosclerotic burden and risk of CVD, evaluate the effects of current and novel therapies and investigate new contributing factors. Many unaccounted factors, both environmental and genetic, may play an important role in the determination of atherosclerosis, underscoring the importance of further cIMT and carotid plaque research investigations for successful prevention and treatment of cardiovascular disease and stroke.

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